CHAPTER 44

Prevention and management of radiation toxicity

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The aim of radiation oncology is the achievement of uncomplicated locoregional control of malignancy by the use of radiation therapy (RT). Accomplishing this goal requires precise knowledge of tumoricidal and tolerance doses of the various normal tissues at risk within the RT field.

Types of RT injury

Radiation injuries can be divided into functional impairment and oncogenesis. There are also different phases of RT injury.

Early effects are usually seen during treatment or within the first few weeks after its completion. These reactions are common, can be significant and symptomatic, but eventually seem to heal completely. Nevertheless, despite what may appear to be total recovery, significant residual damage is often present.

Intermediate effects typically occur several weeks to months after the completion of RT.

Late effects are usually rare and are encountered many months to years after RT. Functional impairments may take a long time to become apparent; an example is memory problems in children who have received cranial irradiation. Oncogenesis is usually a late effect of RT.

Tolerance doses of radiation

Numerous studies have attempted to specify RT tolerance doses for the various tissues and structures of the body. The minimal tolerance dose (TD 5/5) and maximal tolerance dose (TD 50/5) refer to a severe complication rate of 5% and 50%, respectively, within 5 years of RT completion (Table 1). These tolerance doses have been valuable but were drastically revised recently because of the advent of combined-modality therapy (see section on "Combined chemotherapy and irradiation") and altered RT fractionation regimens.

Chemoradiosensitivity of normal tissues Cell-cycle kinetics, mitotic behavior, and differentiation determine the chemoradiosensitivity of normal tissues.

TABLE 1: Normal tissue tolerance to therapeutic irradiation

	TD 5/5 volume[a]			TD 50/5 volume[a]			
Organ	**1/3**	**2/3**	**3/3**	**1/3**	**2/3**	**3/3**	**Selected end point**
Kidneys	5,000	3,000[b]	2,300		4,000[b]	2,800	Clinical nephritis
Bladder		8,000	6,500		8,500	8,000	Symptomatic bladder contracture and volume loss
Bone							
Femoral head			5,200			6,500	Necrosis
TMJ	6,500	6,000	6,000	7,700	7,200	7,200	Marked limitation of joint function
Rib cage	5,000			6,500			Pathologic fracture
Skin			$\frac{100\ cm^2}{5,000}$			$\frac{100\ cm^2}{6,500}$	Telangiectasis
Skin	$\frac{10\ cm^2}{7,000}$	$\frac{30\ cm^2}{6,000}$	$\frac{100\ cm^2}{5,500}$			$\frac{100\ cm^2}{7,000}$	Necrosis/ulceration
Oral mucosa			$\frac{50\ cm^3}{6,000}$			$\frac{50\ cm^3}{7,500}$	Ulcer/fibrosis
Brain	6,000	5,000	4,500	7,500	6,500	6,000	Necrosis/infarction
Brainstem	6,000	5,300	5,000			6,500	Necrosis/infarction
Optic nerve			5,000			6,600	Blindness
Chiasma			5,000			6,500	Blindness
Spinal cord	$\frac{5\ cm}{5,000}$	$\frac{10\ cm}{5,000}$	$\frac{20\ cm}{4,700}$	$\frac{5\ cm}{7,000}$	$\frac{10\ cm}{7,000}$		Myelitis/necrosis
Cauda equina			6,000			7,500	Clinically apparent nerve damage
Brachial plexus	6,200	6,100	6,000	7,700	7,600	7,500	Clinically apparent nerve damage
Eyes (lens)			1,000			1,800	Cataract requiring intervention
Eyes (retina)			4,500			6,500	Blindness
Ears (middle/external)	3,000	3,000	3,000[b]	4,000	4,000	4,000[b]	Acute serous otitis
Ears (middle/external)	5,500	5,500	5,500[b]	6,500	6,500	6,500[b]	Chronic serous otitis

[a] There is insufficient information for recommendations where no values are provided. Clinical judgment and experience are used in these instances, and extrapolation from available information is made.

[b] < 50% of volume does not make a significant change.

Adapted from Emami B, Lyman J, Brown A, et al: Int J Radiat Oncol Biol Phys 21:109-122, 1991; and Rubin P, Casarett GW: Clinical Radiation Pathology, Philadelphia, WB Saunders, 1968.

Organ	TD 5/5 volume[a]			TD 50/5 volume[a]			Selected end point
	1/3	2/3	3/3	1/3	2/3	3/3	
Parotid[b]		3,200[b]	3,200[b]		4,600[b]	4,600[b]	Xerostomia
Larynx	7,900[b]	7,000[b]	7,000[b]	9,000[b]	8,000[b]	8,000[b]	Cartilage necrosis
Larynx		4,500	4,500[b]			8,000[b]	Laryngeal edema
Lungs	4,500	3,000	1,750	6,500	4,000	2,450	Pneumonitis
Heart	6,000	4,500	4,000	7,000	5,500	5,000	Pericarditis
Esophagus	6,000	5,800	5,500	7,200	7,000	6,800	Clinical stricture/ perforation
Stomach	6,000	5,500	5,000	7,000	6,700	6,500	Ulceration/ perforation
Small intestine	5,000		4,000[b]	6,000		5,500	Obstruction/ perforation/fistula
Colon	5,500		4,500	6,500		5,500	Obstruction/ perforation/ ulceration/fistula
Rectum			6,000			8,000	Severe proctitis/ necrosis/fistula/ stenosis
Liver	5,000	3,500	3,000	5,500	4,500	4,000	Liver failure
Testes			± 500			2,000	Sterility
Ovaries			± 300			1,200	Sterility
Vagina			$\frac{5\ cm^3}{9,000}$			10,000	Ulcer/fistula
Pituitary			4,500				Hypopituitarism
Thyroid			4,500			7,000	Hypothyroidism
Muscle			5,000				Clinical myositis
Muscle			10,000				Atrophy
Cartilage (child)			1,000			3,000	Growth arrest
Bone (child)			$\frac{10\ cm^3}{2,000}$			$\frac{10\ cm^3}{2,000}$	Growth arrest

TMJ = temporomandibular joint

TD 5/5 (minimal tolerance dose) and TD 50/5 (maximal tolerance dose) refer to the RT doses required to produce a severe complication rate of 5% and 50%, respectively, within 5 years of RT completion. These RT dose values are used for guidance only and are not absolute. They are modified appropriately depending on the prevailing circumstances.

1/3, 2/3, and 3/3 refer to the approximate volume of organ that is irradiated.

The dividing cell is more vulnerable to RT than the quiescent cell, especially one that is functionally mature.

Dose-limiting organs and tissues have been divided into three classes according to their RT tolerance doses and importance to survival:

- Class I organs are those in which irreparable damage leads to death or severe morbidity.
- Class II organs are those in which damage is associated with moderate morbidity.
- Class III organs are those in which damage produces minimal morbidity.

Combined chemotherapy and irradiation

In combined-modality therapy, several temporal strategies with different rationales are utilized: concurrent RT and chemotherapy, local RT followed by chemotherapy, chemotherapy followed by local RT, and alternating chemotherapy and RT cycles.

POTENTIAL INTERACTIONS

When used in combination, RT and chemotherapy can act independently, with each mode acting in isolation in different parts of the body. The combined use of the two modalities can also result in increased or decreased therapeutic activity, as well as various possible adverse interactions:

- Damaging effects of RT on the target organ can be increased by chemotherapy. Some chemotherapeutic agents are RT enhancers or reactivators, which, when used concurrently with RT, can produce reactions in various tissues at much lower RT doses than expected.
- Damaging effects of chemotherapy on the target organ can be increased by RT.
- Independent injuries can be caused by the individual treatment modality in the same organ, which can combine to increase the resulting dysfunction. Subclinical residual injury from one treatment modality may be uncovered by the subsequent use of a seemingly safe dose of another modality.
- An injury can be produced that is not commonly seen with either modality alone.

The inherent difficulty in understanding these consequences is further complicated by the number of chemotherapeutic agents generally combined in treatment protocols and the variety of conventional or altered RT delivery techniques.

Quantification of treatment toxicity

In addition to therapeutic efficacy, quantification of RT toxicity is crucial for evaluating new regimens and selecting therapy for individual patients. The optimal therapeutic ratio requires not only complete tumor clearance but also minimal residual injury to surrounding vital normal tissues.

Morbidity scoring schemes developed by the Radiation Therapy Oncology Group (RTOG), European Organization for Research and Treatment of Cancer (EORTC), and the National Cancer Institute (NCI) are used most commonly. The late effects of normal tissues (LENT) scoring system was adopted by the RTOG and EORTC in 1995. It graded toxicity according to four parameters, denoted by the acronym "SOMA," which stands for subjective (symptoms reported), objective (signs on examination), management (instituted), and analytic (tissue function assessed by objective diagnostic tools).

In 1997, the NCI with other American (eg, RTOG) and international cooperative groups, the pharmaceutical industry, and the World Health Organization (WHO) revised and expanded the Common Toxicity Criteria (CTC) by integrating systemic agent, radiation, and surgical criteria into a comprehensive and standardized system. The CTC v. 2.0 replaced the previous NCI, CTC, and the RTOG Acute Radiation Morbidity Scoring Criteria.

The third version of the CTC has been renamed Common Terminology Criteria for Adverse Events v. 3.0 (CTCAE v. 3.0). The purpose of renaming it was to move away from the term toxicity, which implies causation and does not fit the jargon commonly used across all modalities. It is anticipated that after October 2003, all NCI-sponsored trials will use CTCAE v. 3.0, which represents the first comprehensive multimodality grading system to include both acute and late effects. The new system is designed for application to all modalities.

TOXIC EFFECTS AND THEIR MANAGEMENT

The incidence and severity of normal tissue toxicity from RT depend on a wide variety of factors, including total dose, fraction size, interval between fractions, quality and type of RT, dose rate, intrinsic radiosensitivity, and specific tissue irradiated. The most common toxic effects seen in different organ systems are outlined here and in Table 2, along with recommended treatments. Where appropriate, the specific effects of chemoradiation therapy are discussed separately.

Head and neck

ORAL MUCOSA

Acute effects Oral mucositis results from radiation-induced mitotic death of the basal cells of the oral mucosal epithelium. It appears about 2 weeks after initiation of RT and can progress from patchy to confluent mucositis.

TABLE 2: Possible irradiation side effects and treatment

Organ	RT side effects	Treatment
Skin	Erythema and dry desquamation	Nonionic moisturizers (eg, Lotionsoft applied tid); topical 1% hydrocortisone cream or ointment applied tid prn, especially for pruritus; Aquaphor; TheraCare cream; vitamin A and E ointment or cream; Biafine, gentle washing; avoid skin irritants
	Moist desquamation	Normal saline compresses or modified Burow's solution soaks before applying creams; polymyxin B/neomycin cream applied tid; Nu-Gel protective wound dressings; antifungal agents for *Candida,* eg, ketoconazole cream; silver sulfadiazine, vitamin A and E ointment
	Ulceration/necrosis	Exclude and treat infections; normal saline compresses; modified Burow's solution soaks; polymyxin B/neomycin cream applied tid; debridement of necrotic tissue, vitamin E (1,000 IU/d) and pentoxifylline (400 mg PO bid-tid); flexible hydroactive dressings (eg, DuoDerm); debriding with fibrinolysin and desoxyribonuclease (eg, Elase)
	Chronic skin changes (eg, skin dryness)	Moisturizers; sun blocks
Oral and oropharyngeal mucosa	Mucositis	Saline/bicarbonate solution oral lavage qid; equal parts of topical viscous lidocaine/diphenhydramine/simethicone mixture for analgesia to swish in mouth or for gargling (5-10 mL qid prn); RadiaCare oral wound rinse; systemic analgesics prn; antifungals; ketoconazole (200 mg/d PO), itraconazole (100-200 mg /d PO), or fluconazole (100-200 mg/d PO) may be helpful; sucralfate suspension (1 g/10 mL), swish and swallow (10 mL PO qid), Gelclair
Esophagus	Esophagitis	Equal parts of topical viscous lidocaine/ diphenhydramine/simethicone mixture for analgesia (5-10 mL PO qid); systemic analgesics prn; nasogastric, gastrostomy, or jejunostomy feeding tube; sucralfate, omeprazole, metoclopramide, or ranitidine sometimes useful especially in the presence of GE reflux
Salivary glands	Sialadenitis/parotitis	Aspirin/NSAIDs
	Xerostomia	Sialogogues; pilocarpine (5 mg PO tid-qid), during and post RT; fluoride gel applications to prevent dental caries; artificial saliva (eg, Salivart, Moi-Stir); amifostine (200 mg/m^2 infused IV over 3 min before daily RT), to protect salivary glands (only in head and neck cancer patients receiving postresection adjuvant RT); Evoxac (30 mg PO tid)

Organ	RT side effects	Treatment
Salivary glands	Thick saliva	Papain enzyme, guaifenesin (Mucinex), and scopolamine patch
Ears	Otitis externa	Hydrocortisone/neomycin/polymyxin B ear drops tid
	Serous otitis media	Decongestants; myringotomy; phenylephrine otic solution
Mandible	Temporomandibular joint fibrosis	Daily stretching exercises
	Osteoradionecrosis	Complete any necessary dental work (especially extractions) before RT; hyperbaric oxygen; eliminate infection with antibiotics; pentoxifylline; perform sequestrectomy only if all else fails
Lungs	Radiation pneumonitis	Prednisone (30-60 mg/d PO for 2-3 weeks), with appropriate tapering
	Pulmonary fibrosis	Supportive measures (eg, oxygen/ bronchodilators), pentoxifylline
Bladder	Acute cystitis	Phenazopyridine (100-200 mg PO tid prn), for dysuria; flavoxate hydrochloride (200 mg PO tid prn), for urinary frequency/urgency; oxybutynin chloride (5 mg PO tid prn), for frequency/urgency
Prostate	Obstructive urinary symptoms	Terazosin hydrochloride or doxazosin mesylate (1-2 mg/d PO); tamsulosin (0.4 mg/d PO); finasteride (5 mg/d PO)
Bowel	Diarrhea	Low-residue diet; loperamide or diphenoxylate (1-2 tabs PO qid prn); exclude *Clostridium difficile* infection; psyllium PO sometimes helpful; cholestyramine (4-8 g PO qid); octreotide (0.1 mg SC tid)
	Proctitis	Anusol-HC cream and Nupercainal ointment perianally or Anusol suppositories per rectum tid prn; psyllium PO sometimes helpful; glucocorticoid retention enemas (eg, Cortenema); mesalamine suppositories (eg, Rowasa); sulfasalazine
Breasts	Erythema and dry desquamation	Nonionic moisturizers (eg, Lotionsoft, TheraCare, Aquaphor applied tid); topical 1% hydrocortisone cream applied tid prn; Biafine, gentle washing; avoid skin irritants
	Moist desquamation	Normal saline compresses or modified Burow's solution soaks before application of creams; polymyxin B/neomycin cream applied tid; Nu-Gel or Telfa protective, nonadherent wound dressings; antifungal agents for *Candida;* silver sulfadiazine to prevent infections; vitamin A and E ointment to promote healing

Spielberger et al compared the effect of palifermin with placebo on the development of oral mucositis in 212 patients with hematologic cancers treated with fractionated total-body irradiation plus high-dose chemotherapy for autologous hematopoietic stem-cell transplantation. The incidence of oral mucositis of WHO grade 3 or 4 was 63% in the palifermin group (6 days' duration) and 98% in the placebo group (9 days duration; $P < .001$). Compared with placebo, palifermin was associated with significant reductions in the incidence of grade 4 oral mucositis (20% vs 62%; $P < .001$), patient-reported soreness of the mouth and throat (area-under-the-curve score, 29.0 vs 46.8; $P < .001$), the use of opioid analgesics (median, 212 mg of morphine equivalents; $P < .001$), and the incidence of use of total parenteral nutrition (31% vs 55%; $P < .001$); *(Spielberger R, Stiff P, Bensinger W, et al: N Engl J Med 351:2590-2598, 2004).*

Regular lavage of the oral cavity with bicarbonate of soda or normal saline solutions (mix 1 tsp of baking soda or 1 tsp of salt with 1 qt of water) is soothing, promotes oral hygiene, and restores normal oral pH. Topical anesthetic mixtures, such as viscous lidocaine, diphenhydramine, and simethicone (in equal parts) and RadiaCare oral wound rinse, may relieve oral discomfort.

Sucralfate suspension (1 g/10 mL) protects the oral mucosa by a coating action; a 10-mL oral dose should be swished and swallowed four times daily. This agent may have a prophylactic benefit and may also aid in the healing process. Fentanyl transdermal (Duragesic) patches or oral transmucosal fentanyl (Actiq) may be necessary for pain control to promote oral intake.

Candida species can colonize the damaged mucosa and exacerbate the mucositis. Oral candidiasis is treated with topical or systemic antifungal agents, such as nystatin (100,000-200,000 U PO qid); ketoconazole (Nizoral, 200 mg/d PO); fluconazole (Diflucan, 100-200 mg/d PO); clotrimazole troches dissolved orally bid-qid; and itraconazole (Sporanox, 100 mg PO bid).

Antibiotics are necessary when superimposed bacterial infection may be present; they may include clindamycin (Cleocin), penicillin V, ciprofloxacin (Cipro), or clarithromycin (Biaxin). Mucosal healing is complete within 2-3 weeks after completion of RT.

Late effects can be characterized by pallor and thinning of the oral mucosa with loss of pliability, submucosal ulceration, and necrosis with exposure of underlying bone and soft tissue. Few interventions are of value once chronic damage has occurred.

Soft-tissue necrosis may be very painful and require systemic or topical anesthetics, eg, viscous lidocaine mixed with equal parts of simethicone and diphenhydramine. Scrupulous hygiene is essential, and antibiotics are used when infection is present. Surgical intervention involves grafting of tissue. Hyperbaric oxygen may promote healing of soft-tissue necrosis.

Effects of chemoradiation therapy The acute ulceration of mucosal epithelium that results from chemoradiation therapy of the head and neck is most severe when both modalities are given simultaneously. Drugs that tend not to produce mucositis, such as cisplatin, are preferable. Percutaneous endoscopic gastrostomy (PEG) tubes are essential to administer nutrition, hydration, and medications during definitive chemoradiation therapy for head and neck malignancies.

Recombinant human keratinocyte growth factor (rHuKGF) effectively reduced the duration of severe oral mucositis in patients undergoing a preparative regimen of total body irradiation, etoposide, and cyclophosphamide (Cytoxan, Neosar) before autologous peripheral stem-cell transplantation (SCT) from 7.7 days to 4.0 days ($P = .001$).

Recent studies continue to show that amifostine is well tolerated and as effective when given subcutaneously as intravenously before irradiation *(Wang R, Kagan RA, Tome MA, et al: Proc Am Soc Clin Oncol [abstract] 22:513, 2003; Samuels MA, Coia LR, Chico I: Proc Am Soc Clin Oncol [abstract] 22:905, 2003)*.

SALIVARY GLANDS

Acute effects Tenderness and marked swelling of the salivary glands (sialadenitis/parotitis) may occur within a few hours after they are first irradiated and usually subside within a few days. These effects can be treated with aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).

Xerostomia Saliva becomes thickened and output decreases during RT, eventually leading to xerostomia. Commencing treatment with a salivary gland stimulant, such as pilocarpine tablets (Salagen, 5 mg PO tid-qid), maintains salivary output during irradiation and lessens morbidity. After completion of RT, pilocarpine stimulates the remaining salivary glands to increase saliva output.

Significant preservation of salivary gland function was found when oral pilocarpine was used concomitantly with curative RT in a phase III randomized study (RTOG 9709), compared with patients for whom pilocarpine was omitted during RT. This finding indicates a prophylactic effect on irradiated salivary glands by pilocarpine.

Amifostine (Ethyol) is now approved by the US Food and Drug Administration (FDA) as a salivary gland radioprotector in head and neck cancer patients who have undergone a complete resection of their cancer and will be receiving adjuvant RT that includes the parotid salivary glands. Amifostine (200 mg/m^2) is administered daily as a 3-minute IV infusion 15-30 minutes before standard RT (1.8-2.0 Gy) to reduce the incidence of moderate to severe xerostomia in patients in whom the radiation field includes the parotid glands.

Glyceride, baking soda, guaifenesin (Mucinex), scopolamine patch, and carbonated drinks may improve the acute problems caused by thickened saliva. Always ensure that patients being treated with RT are adequately hydrated. Dehydration makes saliva thicker and reduces output. Papain, the proteolytic enzyme found in papayas, helps dissolve thick saliva.

Chronic effects Xerostomia may persist for months to years, with recovery depending on the volume irradiated, the total RT dose, and individual patient variation. Xerostomia is treated with saliva substitutes and sialogogues, including water and glycerin preparations, commercially prepared "artificial saliva" (eg, Salivart, Xero-Lube, Moi-Stir), and salivary gland stimulants (eg, bromhexine and pilocarpine tablets).

Cevimeline (Evoxac) is being assessed for efficacy and safety in the treatment of radiation therapy-induced xerostomia. It is presently FDA-approved for Sjögren's syndrome.
The dose is 30 mg PO tid.

Daily pilocarpine (15-30 mg in divided doses) may be administered following RT to increase salivary output. Early improvement may be observed, but up to 12 weeks of uninterrupted therapy may be necessary to assess whether a beneficial response will be achieved.

TASTE BUDS

Some patients experience loss of food flavor during the acute mucosal reaction to RT, due to damage of the taste bud cells. These cells are capable of repopulating within 4 months after treatment, but some degree of permanent impairment may remain. Sour and bitter tastes are suppressed to a greater extent than are sweet and salty tastes. Xerostomia and mucositis also contribute to the dysgeusia.

EXTERNAL AND MIDDLE EAR

Inflammatory changes in the external auditory meatus and middle ear occur during RT or soon thereafter and may be manifested by pain, infection, or decreased hearing. Hydrocortisone/neomycin/polymyxin B ear drops or benzocaine/antipyrine/phenylephrine otic solution (Tympagesic) may be used for otitis externa. Decongestants and/or antihistamines, eg, pseudoephedrine/triprolidine, pseudoephedrine/guaifenesin, astemizole (Hismanal), and fexofenadine (Allegra), are useful for otitis media, but occasionally myringotomy is performed to relieve discomfort. Possible superimposed infections are treated also with oral antibiotics, eg, clarithromycin and amoxicillin/potassium clavulanate (Augmentin).

PHARYNX AND ESOPHAGUS

Pharyngitis and esophagitis with resultant dysphagia develop 2-3 weeks after RT commencement. Dysphagia usually resolves 2-3 weeks after the completion of irradiation (see also section on the esophagus in "Gastrointestinal system" later in this chapter).

Oral topical (see previous section on "Oral mucosa") or systemic analgesics are used to provide relief and enable adequate nutrition. Sucralfate suspension is useful as a mucosal protective coating agent and may promote healing. A nasogastric, gastrostomy, or jejunostomy tube may be necessary for nutritional support.

SKELETON AND SOFT TISSUES

Mandible Irradiation can diminish the ability of bone to withstand trauma and avoid infection, with resultant osteoradionecrosis (a hypovascular, hypocellular dissolution of bone). Important risk factors include poor nutrition and oral hygiene, trauma (especially dental extractions), continued tobacco and alcohol consumption, RT quality, total dose, overall duration, and frequency (daily vs bid). To decrease the risk of these adverse effects, any necessary dental work (especially extractions) should be performed at least 10 days prior to the initiation of RT.

Dental extractions performed after RT must be done judiciously, since they may initiate osteoradionecrosis. Hyperbaric oxygen may be useful prior to teeth extractions from heavily irradiated bones. It is also used to aid healing in established cases of osteoradionecrosis. Pentoxifylline improves blood flow.

Infection can expand the area of necrosis and cause severe pain. Antibiotics (eg, clarithromycin, ciprofloxacin, and amoxicillin/potassium clavulanate) are often necessary and require long-term administration. Sequestrectomy is performed only if all conservative measures have failed.

Teeth Loss of adequate saliva for food lubrication and buffering of acids can lead to multiple problems, including dental caries. Optimal oral and periodontal hygiene must be maintained indefinitely. Daily topical fluoride applications, preferably a fluoride gel held in contact with the teeth by a tray, are extremely effective. Attempts should be made to replace or increase salivary flow (see previous section on "Salivary glands").

Okunieff et al studied the effects of pentoxifylline (400 mg po tid) on 30 patients with irradiation-induced fibrosis at 1 to 29 years after 40 to 84 Gy of radiotherapy. The primary outcome measurement was change in physical impairments secondary to irradiation, including active and passive range of motion (AROM and PROM), muscle strength, limb edema, pain, and plasma levels of tumor necrosis factor alpha and fibroblast growth factor 2 (FGF2). After 8 weeks of pentoxifylline intervention, 20 of 23 patients with impaired AROM and 19 of 22 with impaired PROM improved; 11 of 19 patients with muscle weakness showed improved motor strength; 5 of 7 patients with edema had decreased limb girth; 9 of 20 patients had decreased pain. Pretreatment FGF2 levels dropped from an average of 44.9 pg/mL to 24.0 pg/mL after 8 weeks of treatment (*Okunief P, Augustine E, Hicks, JE, et al: J Clin Oncol 22:2207-2213, 2004*).

Temporomandibular joint (TMJ) Masticatory muscle and TMJ fibrosis can result in trismus. Stretching exercises may alleviate this problem. The Therabite jaw motion rehabilitation system provides anatomically correct motion of the jaw to patients experiencing hypomobility of the mandible. It consists of a mouthpiece and lever that exerts appropriate force to increase the interdental gap.

Soft tissues Soft-tissue necrosis is rare but may occur after insertion of an ill-fitting prosthesis or treatment with a very high local dose of radiation, as is delivered by an interstitial implant. Conservative management includes oral hygiene, antibiotics, pentoxifylline, and hyperbaric oxygen.

Irradiation of the neck, by itself, produces little or no impairment of function but in the postoperative setting may exacerbate surgically induced limitations of head and neck motion by up to 20%. Physical therapy prevents contractures. Patients should stretch the affected area prophylactically several times a day. This practice is especially useful in preventing trismus.

LARYNX

Edema of the arytenoids may occur after a course of RT to the larynx. It may be managed conservatively by resting the voice and administering antibiotics and steroids. Pentoxifylline may also be tried. Edema persisting for more than 3 months following RT may be due to recurrent or persistent tumor.

HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen (HBO) has been used for more than half a century to treat associated late complications of irradiation. The European Society for Therapeutic Radiotherapy and Oncology and the European Committee for Hyperbaric Medicine organized a consensus conference in 2001 to deal with the indications of HBO for the treatment and prevention of late complications from irradiation. A systematic literature search was performed at the time. The review was updated recently to include the years 1960 and 2004. Hyperbaric oxygen treatment involving complications to the head and neck, pelvis, and nervous system and the prevention of complications after surgery in irradiated tissues was studied. Despite the small number of controlled trials, HBO was recommended for the treatment of mandibular osteoradionecrosis in combination with surgery and hemorrhagic cystitis resistant to conventional treatments. The most significant level of evidence seemed to be for the prevention of osteoradionecrosis after dental extractions.

Bui et al investigated the efficacy of HBO in 45 patients with irradiation-induced late side effects, for whom previous interventions had failed in most of them. Improvement of principal presenting symptoms after HBO was noted in 75% of head and neck, 100% of pelvic, and 57% of "other" subjects (median duration of response was 62, 72, and 69 weeks, respectively). Bone and bladder symptoms were most likely to benefit from HBO (response rate, 81% and 83%, respectively). Half of subjects with soft-tissue necrosis or mucous membrane side effects improved with HBO. A low response rate was seen with salivary (11%), neurologic (17%), and upper gastrointestinal symptoms (22%). The incidence of relapse was low (22%), and minor HBO-related complications occurred in 31% of patients.

Komaki et al randomized two groups of 62 patients in total with inoperable nonmetastatic non–small-cell lung cancer: arm 1 and arm 2 received concurrent cisplatin-based chemotherapy and radiotherapy (RT), but arm 2 received amifostine also. Amifostine reduced the severity and incidence of acute esophageal, pulmonary, and hematologic toxicity resulting from the chemotherapy and RT. Maximal esophageal toxicity was mild (grade 1) in 23%, moderate (grade 2) in 42%, and severe (grade 3-4) in 35% of patients in arm 1; the corresponding rates for arm 2 patients were 48%, 35%, and 16% respectively (P = .021). Severe pneumonitis occurred in 16% of patients in arm 1 and in none of the arm 2 patients (P = .020, chi-square test). Neutropenic fever occurred in 39% of arm 1 patients and 16% of arm 2 patients (P = .046, chi-square test; *Komaki R, Lee JS, Milas L, et al: Int J Radiat Oncol Biol Phys 58:1369-1377, 2004*).

Lungs

Radiation pneumonitis When doses of thoracic RT exceed tolerance levels, pulmonary reactions are expressed clinically as a pneumonitic process 1-3 months after the completion of therapy. This process can prove lethal if both lungs are involved or if threshold doses of chemotherapeutic drugs have been exceeded. Recovery from acute pneumonitis usually occurs, and the second phase of fibrosis follows almost immediately, with eventual progression to the late fibrotic phase.

Acute symptoms include low-grade fever, congestion, cough, dyspnea, pleuritic chest

pain, and hemoptysis. Evidence of consolidation may be found in the region corresponding to the pneumonitis. The acute pneumonitic phase is relatively short-lived but can be severe. Chest x-ray and CT show a diffuse infiltrate corresponding to the RT field.

Management Optimal management is clearly prevention. Corticosteroids can foster recovery from acute RT pneumonitis; a dose of 30-60 mg of prednisone is administered daily for 2-3 weeks and then tapered. Antibiotics for proven infection and supplemental oxygen may be necessary.

In recent phase III randomized trials of lung cancer patients treated with chemoradiation therapy, amifostine significantly reduced acute pneumonitis from 23% to 3.7% ($P = .037$), without any reduction in tumoricidal activity.

Pulmonary fibrosis develops insidiously in the previously irradiated field and stabilizes after 1-2 years, with most patients being asymptomatic. Symptoms are proportional to the extent of lung parenchyma involved and the preexisting pulmonary reserve and are generally minimal if fibrosis is limited to < 50% of one lung. If fibrosis exceeds this limit, dyspnea associated with progressive chronic cor pulmonale may become clinically manifest.

Radiologic changes consistent with fibrosis are usually seen. Retraction of the involved lung with elevation of the hemidiaphragm are the two predominant findings. CT scanning is currently favored for imaging this region. Pulmonary function tests may show mild deterioration as fibrosis develops. Significant changes are not seen when small volumes of lung tissue are irradiated due to functional compensation from adjacent lung regions. Diffusion capacity studies provide the best assessment of whole lung function.

Management Radiation-induced fibrosis presently appears to be irreversible. Management consists of supportive measures, such as oxygen, bronchodilators (ie, albuterol), and ipratropium (Atrovent). Counseling on the risks of smoking is imperative. Pentoxifylline with vitamin E has recently been shown to cause regression of RT-induced fibrosis.

Effects of chemoradiation therapy The pneumonitis and fibrosis associated with RT can also be seen with several chemotherapeutic drugs, including bleomycin, methotrexate, mitomycin (Mutamycin), nitrosoureas, alkylating agents, and vinca alkaloids. Obviously, these agents can potentiate the damaging effects of RT on the lungs.

Cardiovascular system

PERICARDIAL DISEASE

Acute pericarditis is a rare complication of RT that usually follows irradiation of a radiosensitive mass contiguous to the heart. Signs and symptoms are similar to those of acute, nonspecific pericarditis and include chest pain, fever, and, often, electrocardiographic (ECG) abnormalities.

Pericardial effusion Chronic pericardial effusion may be asymptomatic or lead to cardiac tamponade, which must then be relieved by pericardiocentesis or pericardiectomy.

Pericardial constriction can occur as a final stage of either of the two pericardial syndromes or may develop insidiously without an obvious antecedent event.

MYOCARDIAL DISEASE

Pancarditis Patients treated with RT alone can develop cardiomyopathy and present with severe signs and symptoms of pericardial disease, along with constriction and severe heart failure. Pathologically, there are alterations in the pericardium and myocardium. This condition has been termed "pancarditis." Radiation myocardiofibrosis may occur to a minor degree in asymptomatic patients.

Radiation cardiomyopathy is uncommon with modern treatment techniques unless tolerance doses are exceeded. Simultaneous or sequential chemotherapy (especially with the anthracyclines) aggravates the condition. The interaction between the two modalities appears to be additive. Risk factors for anthracycline cardiotoxicity are other types of heart disease, such as valvular, coronary, or myocardial lesions and hypertension, as well as age > 70 years.

Management The best treatment is clearly prevention. In patients treated with RT and concomitant or sequential doxorubicin, downward adjustment of tolerance doses is appropriate. Dexrazoxane (Zinecard) is a cardioprotective agent used in the prevention and reduction of cardiotoxicity that can be associated with doxorubicin. Dexrazoxane has been shown to reduce doxorubicin-induced cardiomyopathy and allows administration of higher doses of doxorubicin in randomized trials. No evidence has shown an adverse effect of dexrazoxane on the antitumor activity of doxorubicin.

CORONARY ARTERY DISEASE

Radiation-induced coronary artery disease has the same clinical manifestations as are observed in patients who have not received RT. Treatment, including coronary artery bypass surgery, is also the same.

VALVULAR DEFECTS AND CONDUCTION ABNORMALITIES

Other cardiac problems attributed to RT include valvular defects (due to myocardial fibrosis adjacent to valves) and conduction abnormalities (due to ischemic fibrosis of the conduction system).

Skin

Acute effects The acute skin reaction occurs during the first 7-10 days following RT and begins with erythema, progressive pigmentation, epilation, and desquamation as the dose increases. Dry desquamation may then progress to moist desquamation, which usually heals by 50 days following RT; however, it may not heal completely and even may progress to necrosis.

Management Symptomatic treatment that controls pain, keeps the radiation field clean, and removes the crust suffices until epithelial remodeling and reepithelialization restore the skin to normal. Daily normal saline compresses or modified Burow's solution soaks are useful. Topical hydrocortisone creams and nonionic moisturizers, such as Lotionsoft, TheraCare, Biafine, and Aquaphor, are used to alleviate pruritus and the acute inflammatory response to irradiation, whereas antibiotic agents and silver sulfadiazine are prescribed to prevent infection in areas of moist desquamation.

Patients should be advised to wash their skin gently and dry it by dabbing. Irritating skin products should be avoided. Nu-Gel protective wound dressings can also be used; they provide a soothing sensation when cooled. Telfa nonadhesive pads are used to protect the wound. Vitamin A and E ointment or cream promotes healing. Silver sulfadiazine cream and antibiotic creams prevent infection.

Late effects occur many weeks following RT. A variable period during which the skin appears normal follows the acute reaction. Scaling, atrophy, telangiectasis, subcutaneous fibrosis, and necrosis can then develop and progress for long periods. Telangiectasis develops in an atrophic dermis under a thin epidermis as an area of reddish discoloration displaying multiple, prominent, thin-walled, dilated vessels. Fibrosis is characterized by progressive induration, edema, and thickening of the dermis and subcutaneous tissues and is most severe in areas where there was an earlier moist desquamation.

Management Permanent use of skin moisturizers may be necessary, and irradiated skin must always be protected from the sun. Medical management of chronic ulcers is directed at relieving symptoms and treating infections while attempting to promote healing. Surgical management consists of excision and grafting of the irradiated area. Laser treatment of telangiectasis improves cosmesis. Pentoxifylline (400 mg PO bid-tid) increases blood velocity and may promote healing. One clinical trial showed striking regression of chronic radiotherapy-induced fibrosis in patients after they were treated for at least 6 months with pentoxifylline (400 mg bid) and tocopherol (vitamin E), 1,000 IU/d.

Effects of chemoradiation therapy An additive response between chemotherapy and RT should be anticipated. An increased erythematous response is seen in breast cancer patients receiving combined therapy that includes methotrexate.

The most consistent aggravated skin responses occur in patients with anal, vulvar, or penile carcinoma who receive RT and fluorouracil (5-FU). The first reaction, which occurs following the initial infusion of 5-FU during the first week of RT, is mild. The acute moist reaction produced after the second infusion of 5-FU and the higher accumulated RT doses is more severe. It involves the entire field but heals after a few weeks. Similar reactions are noted in patients with head and neck cancer who receive chemoradiation therapy.

Central nervous system

BRAIN

Acute effects are rare during conventionally fractionated brain RT. Acute encephalopathic changes have been noted in conjunction with several cytotoxic agents, including cisplatin, asparaginase (Elspar), ifosfamide (Ifex), methotrexate, cytarabine (Ara-C), interferon, and interleukin-2 (IL-2 [Proleukin]). Clinical changes include alteration of mental status or level of consciousness, focal worsening of neurologic signs, and/or generalized seizures. These changes are commonly thought to be due to RT-induced edema and are usually treated adequately with concomitant corticosteroid administration.

Subacute or early delayed reactions Two types of subacute or early delayed reactions have been observed after RT.

Somnolence syndrome is noted 2-6 months after RT and is characterized by somnolence, anorexia, and irritability without accompanying focal neurologic abnormalities. The syndrome is usually transient (resolving within 2-5 weeks), associated with an uneventful recovery, and thought to be due to demyelination following a temporary inhibition of myelin synthesis. The somnolence syndrome is commonly seen after cranial RT for childhood acute lymphocytic leukemia (ALL). Similar transitory, self-limited changes of fatigue and/or exacerbation of focal neurologic signs are noted following full cranial or local RT for primary CNS tumors.

Focal neurologic signs seen after the treatment of CNS tumors may be related to intralesional reactions and are probably indicative of tumor response and/or perilesional reactions, such as edema or demyelination. These signs may be associated with imaging changes, such as focal enhancement, indicating areas of blood-brain barrier disruption and inhomogeneity in the white matter. New RT techniques appear to be frequently associated with subacute CNS reactions.

Clinical deterioration and MRI changes representing intralesional necrosis with diffuse pontine swelling have occurred in up to 40% of patients 1-6 months after hyperfractionated RT for brainstem gliomas. High-dose, volume-limited stereotactic radiosurgery is followed by transient white matter alterations, often apparent on MRI. These abnormalities generally begin ≥ 6 months after RT and are usually self-limited. Similar phenomena have been reported following interstitial brain implants.

Late effects Various late CNS effects have been described following RT.

Focal radiation necrosis Localized necrosis develops between 6 months and 2 years following irradiation. New anatomically related functional/irritative signs and symptoms are seen, associated with increasing intracranial pressure.

CT changes are usually confined to the high-dose volume and include low-density white matter changes with irregular enhancement, often associated with surrounding diffuse edema and a variable degree of mass effect. MRI shows similar local changes associated with more extensive areas of white matter alterations, including edema. Differentiating necrosis from tumor

recurrence/progression is usually difficult. ^{18}Fluorodeoxyglucose (FDG)-PET scans indicate hypometabolic findings.

Corticosteroids and surgical resection of focal areas of radiation necrosis can result in clinical improvement of neurologic deficits.

Postirradiation diffuse white matter injury Low-density changes diffusely involving one or both cerebral hemispheres may be evident within several months following full-brain RT. It is common to see white matter alterations extending peripherally beyond the high-dose RT volume.

MRI is more sensitive than CT to white matter changes and shows injury initially limited to periventricular white matter and later extending to include most of the rest of the cerebral white matter. Ventricular dilatation and cortical atrophy are seen with more severe white matter injury.

Symptoms vary widely from mild lassitude or personality changes to marked, incapacitating dementia. Progressive memory loss precedes frank dementia in cases with pronounced ipsilateral or diffuse bilateral changes.

Combined-therapy diffuse white matter injury/leukoencephalopathy In its milder forms, this syndrome is characterized by transient lassitude, dysarthria, or seizures temporally related to the administration of prophylactic cranial RT and methotrexate in children with ALL. The syndrome appears to be continuous, with more severe CNS damage (including progressive degrees of ataxia, confusion, and memory loss) ultimately leading to dementia or death. More recently, similar clinical events of varying severity have been noted 12-18 months after treatment in adults surviving intensive chemotherapy and prophylactic cranial irradiation (PCI) for small-cell lung carcinoma (SCLC).

Imaging findings are similar to those previously noted for postirradiation diffuse white matter injury. Dystrophic calcifications (mineralizing microangiopathy) are noted as late changes in leukoencephalopathy and are most often limited to the basal ganglia and gray-white matter interface.

Neuropsychologic effects Intellectual impairment has been reported increasingly among long-term cancer survivors. Cognitive changes in children are marked by memory deficits and learning disabilities. Memory deficits are apparent by 6 months, whereas a decline in global IQ is more often noted beyond 1-2 years after treatment. Neurocognitive impairment is most pronounced in children < 4-7 years old. Deterioration in IQ is statistically significant primarily in children following full-brain or supratentorial RT for primary CNS tumors.

Retrospective studies have reported neurotoxicity in approximately 19% of long-term survivors of SCLC who received PCI and chemotherapy. Problems include memory loss, confusion, dementia, ataxia, psychomotor retardation, and optic atrophy. Discernible intellectual decline is first seen at 4-6 months after therapy and becomes more pronounced 2-3 years later. These studies did not assess neuropsychologic function before RT was administered. Other studies that have assessed similar patients' neuropsychologic function before and after PCI have not found any evidence of neurotoxicity.

Cerebrovascular effects Arterial cerebrovasculopathy is an infrequent effect that occurs almost exclusively following RT to the parasellar region. Single- or multiple-vessel narrowing/obliteration results in deficits typical of stroke. Vasculopathy is usually related to RT for optic chiasmatic/hypothalamic gliomas in children.

Radiation-induced neurologic tumors Most RT-induced gliomas occur in patients who were irradiated as children and young adults. The 30-year cumulative risk for these tumors is about 0.8%.

SPINAL CORD

Transient radiation myelopathy has an incidence of approximately 15%, with a latency period of 1-29 months after RT, and is seen especially in patients who received mantle-field RT for Hodgkin's lymphoma. This syndrome is due to transient demyelination in the posterior columns and/or lateral spinothalamic tracts within the RT field.

Patients experience sudden electric-like shocks radiating from the spine to the extremities on neck flexion (Lhermitte's sign); these shocks are usually symmetrical and unrelated to a specific dermatome. Neurologic examination is otherwise normal. The clinical picture reverses spontaneously after an average of about 5 months.

Delayed radiation myelopathy Patients present with a several month history of progressive neurologic signs and symptoms, such as paresthesias and decreased pain and temperature sensation. A bimodal frequency distribution of latency has been reported, with peaks at 13 and 26 months, possibly corresponding to white matter parenchymal and vascular damage, respectively. Symptoms usually progress over 6 months and involve all spinal cord systems but may develop acutely following infarction of the spinal cord.

Temporary remissions have been reported following treatment with steroids or hyperbaric oxygen, but about 50% of patients die of secondary complications. Larger daily RT fractions, decreased number of treatments, treatment of larger lengths of spinal cord, and high total doses increase the risk of RT-induced myelopathy.

Effects of chemoradiation therapy Although experimental data are sparse, simultaneous administration of RT and chemotherapeutic agents known to be neurotoxic (eg, methotrexate, cisplatin, vinblastine, and cytarabine) may further reduce spinal cord tolerance. Intrathecal chemotherapy can produce myelopathy; thus, its use in combination with RT clearly must be approached with caution. Studies of hyperfractionated RT regimens have shown the spinal cord to be the dose-limiting organ. The interval between RT fractions should be at least 6 hours and preferably longer.

Eyes and adnexa

OCULAR ADNEXA AND ANTERIOR SEGMENT

Acute effects include transient skin erythema, conjunctivitis, epilation of hair follicles in the irradiated field, and chemosis. The cornea develops epithelial edema, leading to punctate epithelial keratopathy. Perilimbal injection may be seen with mild keratouveitis. Treatment involves artificial tear drops and topical steroids. Antibiotic eyedrops may be added to prevent or treat infection.

Late effects result in chronic structural changes, such as trichiasis, closure of eyelid puncta, and ectropion or entropion. Skin changes can progress in some areas to pallor, atrophy, telangiectasis, and loss of the eyelashes. Keratitis sicca (dry eye syndrome) may be caused by damage to the lacrimal, goblet, meibomian, and accessory lacrimal glands, which are essential to adequate tear film production. Epiphora may be due to excessive tearing from reflex aqueous production in response to keratitis sicca but may also herald closure of the nasolacrimal drainage system.

Management of epiphora is directed toward determining the cause of the chronic tearing and treating the underlying pathology. Keratitis is managed with aggressive lubrication (Celluvisc, Lacrilube, Lacinsent), eye patching, and antibiotic drops to prevent recurrent corneal erosions.

LENS

Radiation induces cataracts by damaging the germinal zone of the lens epithelium; this damage usually presents as subcapsular opacifications. The frequency, latency, and progression of lens opacities are a function of RT dose and fractionation. Prevention of damage with customized lens shields during RT is clearly the best management.

RETINA

Radiation-induced retinopathy is caused by an occlusive microangiopathy, which is manifested by cotton wool exudates, microaneurysms, telangiectasis, retinal hemorrhage, macular edema, proliferative neovascularization, vitreous hemorrhage, and pigmentary changes. Central retinal artery and vein occlusion have been described. Incomplete perfusion of the capillary bed, as shown by fluorescein angiography, is the most consistent finding. Visual symptoms depend on the retinal area that has been damaged. Radiation-induced and diabetic retinopathies are similar pathologically.

An Hellenic group trial randomized patients with pelvic malignancies (rectal, 32; bladder, 47; prostate, 40; gynecologic, 86) to receive radiation therapy (RT) ± amifostine. Patients received radical RT (65-70 Gy) or postoperative RT (50 Gy). Significant reduction occurred in acute grade 2/3 bladder and lower GI tract toxicities in the amifostine group ($P < .05$, weeks 3-7) without evidence of tumor protection (*Athanassiou H, Antonadou D, Coliarakis N, et al: Int J Radiat Oncol Biol Phys 56:1154-1160, 2003*).

Argon panretinal photocoagulation has resulted in regression of fibrovascular neovascularization. Focal and grid macular treatment can stabilize the progression of visual loss in some patients with macular edema.

OPTIC NERVE

Radiation optic neuropathy (RON) presents as sudden, painless, monocular loss of vision. Visual-field abnormalities usually associated with RON include optic nerve fiber bundle defects and central scotomas.

Effective treatment for RON has not been identified. Prevention is most important and is accomplished by avoiding large single fractions in stereotactic radiosurgery and short intense schedules comprising large fractions.

SECONDARY NEOPLASMS

Children with heritable retinoblastoma have a cancer diathesis, and RT further increases this risk. The most common tumor occurring within the RT field is osteosarcoma of the facial bones. Other secondary neoplasms reported include soft-tissue sarcomas, brain tumors, leukemia, and melanoma.

Bladder, urethra, and ureter

Bladder injury may be either global or focal. Symptoms of global injury include urinary frequency, urgency, decrease in bladder capacity, and cystitis. Symptoms of focal injury include bleeding, ulceration, stone formation, and fistulas.

Acute RT cystitis presents with symptoms of dysuria and urinary frequency and urgency. The incidence varies widely, depending on factors related to radiation timing, dose, and volume. Acute symptoms subside within several weeks following RT.

Management is generally symptomatic. Phenazopyridine (Pyridium) is used as a topical analgesic for dysuria. Oxybutynin (Ditropan), an antispasmodic that relaxes bladder smooth muscle by inhibiting the muscarinic effects of acetylcholine, is useful in relieving symptoms of urinary frequency and urgency. Flavoxate (Urispas) and hyoscyamine counteract bladder muscle spasm.

Terazosin (Hytrin) and doxazosin (Cardura), both at 1-2 mg PO daily, may be used in prostate cancer patients who develop obstructive urinary symptoms during pelvic RT. Tamsulosin (Flomax) and finasteride (Proscar) are also used in these patients.

Late effects The interval between RT and the onset of late complications is several months to years, with a median of approximately 13-20 months. Most bladder complications occur within 2-3 years of therapy and include decreased bladder capacity, hematuria from telangiectasis, chronic irritative or obstructive urinary symptoms, and fistulas.

Urethral strictures occur more frequently when there is a history of transurethral resection of the prostate. Defects in urethral resistance are less common

than strictures. Severe sphincteric insufficiency may be managed with periurethral injection of polytetrafluoroethylene collagen. Patient-controlled low pressure sphincters may be placed surgically. Urethral strictures are most often managed with simple endoscopic incision or open surgical repair.

Ureteral injury is rarely seen and is reported primarily following pelvic RT and chemotherapy. The length of the ureter irradiated, the presence of tumor, and surgical manipulation all affect tolerance of the ureter to RT.

Management The assessment and management of bladder dysfunction after RT, with or without chemotherapy, require adequate evaluation, including radiography and urodynamics to determine the precise cause of the dysfunction. Drugs to increase bladder storage include propantheline (Pro-Banthine), oxybutynin, and imipramine. Drugs to increase outlet resistance include ephedrine, pseudoephedrine, and phenylpropanolamine. Severe reductions in bladder capacity that do not respond to pharmacotherapy may be managed with bladder augmentation using a segment of intestine.

Severe hemorrhage caused by RT complications should be treated with cystoscopy and selective cauterization of bleeding sites, followed by irrigation with various agents, such as alum, silver nitrate, or dilute formalin.

Female reproductive system

VULVA

Acute effects Acutely, the vulva demonstrates erythema, which progresses to confluent moist desquamation that is radiation volume- and dose-dependent. The reaction is greatest in the intertriginous areas. Acute effects resolve 2-6 weeks after completion of RT. Skin edema of the vulva and mons pubis may develop 1-3 months after treatment. It is usually painless but can be severe and become chronic. Streptococcal lymphangitis may also develop.

Late effects develop 6-12 months following RT and include vulvar skin thinning, atrophy, dryness, pain, pruritus, and telangiectasis. Epilation is usually complete, and increased skin pigmentation may also develop. Fibrosis of the underlying subcutaneous tissues can result in dyspareunia if it involves the clitoris or vaginal introitus. Painful late ulceration with chronic serous drainage 1-2 years after RT may also occur.

Management The key to management of vulvar skin reactions is aggressive, individualized personal hygiene. Twice-daily sitz baths and gentle skin cleansing should be followed by complete drying of the vulvar region. The best method for drying the skin is a small fan or hair dryer (cool setting). This regimen should be closely followed until the skin is completely healed.

Topical steroid and antibiotic creams are applied for symptomatic relief and to prevent infection, respectively (see previous section on "Skin"). Whirlpool baths may be beneficial. Ulceration or necrosis requires debridement, which should continue until granulation tissue has formed. Myocutaneous flaps may be necessary.

Atrophic vulvar skin, once healed, may benefit from topical estrogen or testosterone creams. Daily dilatation to prevent fibrotic stenosis of the introitus may be necessary.

VAGINA

Acute effects Erythema, moist desquamation, confluent mucositis, severe congestion, and submucosal hemorrhage can be seen acutely and may resolve within 2-3 months after irradiation. Some patients demonstrate progressive vascular damage and ischemia, which result in epithelial sloughing, ulcer formation, and necrosis. These changes may require 4-8 months to heal.

Late effects include thinning and atrophy of the vaginal epithelium with development of telangiectasis. Reduced vaginal capacity due to fibrosis and decreased lubrication results in dyspareunia. Thin, filmy adhesions or synechiae develop and can become permanent, with fusion of the vaginal walls (agglutination) if not managed appropriately. Vaginal ulceration or necrosis may develop several months following RT.

Management Acute RT vaginitis is managed with vaginal douching (using a mixture of 1 part hydrogen peroxide to 10 parts water 2-3 times daily until resolution). Daily vaginal dilatation is required once the acute reaction has resolved to prevent vaginal stenosis. Intravaginal estrogen cream appears to stimulate epithelial regeneration and may be used twice weekly to promote healing, prevent vaginal mucosal atrophy, and improve lubrication and elasticity.

Fistula formation may be treated with periodic debridement and antibiotics. Urinary and fecal diversion is sometimes required, with delayed reanastomosis and myocutaneous grafting for repair.

CERVIX AND UTERUS

Superficial ulceration of the cervix is an inevitable consequence of RT for carcinoma of the cervix that may persist for months, resulting in a thin, clear vaginal discharge.

Cervical os stenosis occurs 3-6 months following high-dose brachytherapy for cervical and endometrial carcinoma.

Rare complications Rarely, hematometra can develop due to residual functioning endometrium, which responds to hormonal stimulation. There is consequent retention of hemorrhagic debris because of obliteration of the endocervical canal or cervical os stenosis. True necrosis of the endometrial cavity also occurs rarely following RT for endometrial carcinoma. An uncommon complication of pelvic RT is development of high-grade endometrial carcinoma or uterine sarcoma many years after therapy.

Management Cervicitis, ulceration, and necrosis of the cervix are managed with douching (1 part hydrogen peroxide to 10 parts water 2-3 times daily until resolution) and debridement as necessary. Dilatation of the stenotic cervical os may be necessary to prevent hematometra or, in the case of uterine necrosis, to allow drainage of necrotic material.

OVARIES AND REPRODUCTIVE/ENDOCRINE FUNCTION

Hormonal changes Premenopausal women with intact ovaries exposed to sufficiently high RT doses experience premature menopause. In a North Central Cancer Treatment Group (NCCTG) randomized trial, venlafaxine (Effexor) has been found to substantially reduce hot flashes in women with breast cancer experiencing menopausal symptoms and in whom estrogen and progesterone preparations are contraindicated.

Ovarian carcinoma following pelvic RT for carcinoma of the cervix is extremely uncommon.

Sexual dysfunction is a frequent occurrence following surgery, RT, and chemotherapy for pelvic malignancies and results in psychosexual problems.

Management The ovaries can be protected by moving them away from areas that are to be irradiated. A sexual function history should be obtained from all patients at 3 months after RT using one of the several available psychologic instruments. Interventions include improving personal hygiene, hormones, vaginal lubrication, and routine use of a vaginal dilator. Hormonal replacement is accomplished with oral conjugated estrogens or estradiol patches (Estraderm) and progesterone as necessary.

Male reproductive system

Testicular dysfunction following RT includes azoospermia, oligospermia, and hormonal changes. Recovery of sperm count may take months to years. Oligospermia occurs after very low doses of RT. It may therefore be precipitated by exposure to scattered RT from other treatment sites, as well as by total-body RT used as a conditioning regimen for bone marrow transplantation (BMT). Sterility develops at higher RT doses. Erectile dysfunction is seen in patients receiving high RT doses to the pelvis, as for prostate cancer.

Management The best management is prevention by appropriate RT field tailoring and shielding. Sperm-banking should always be carried out if there are fertility concerns. Sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis) are available for impotent patients.

Gastrointestinal system

LIVER

Radiation- and chemotherapy-induced liver disease The chief hepatic toxicity of chemotherapy and RT is subacute, beginning 7-90 days after completion of therapy. There are many similarities between radiation-induced liver disease (RILD) and combined modality-induced liver disease (CMILD). Pathologically, the common lesion for both is veno-occlusive disease (VOD).

RILD occurs approximately 4-8 weeks after the completion of RT. Symptoms include fatigue, rapid weight gain, increased abdominal girth, and right upper quadrant discomfort. Patients are rarely jaundiced and may develop ascites

and hepatomegaly with elevated alkaline phosphatase levels out of proportion to other hepatic enzymes. CT scan shows low density in the irradiated region of the liver.

CMILD differs from RILD in some respects, with the most distinctive differences being the faster onset of the former and the early expression of jaundice. Liver enzymes are mildly increased, and bilirubin levels are significantly elevated. As CMILD produces no distinctive changes on imaging studies, the diagnosis is one of exclusion.

CMILD is most commonly seen in the setting of allogeneic BMT, which requires aggressive preparative techniques involving administration of both high-dose chemotherapy and total-body RT. Patients present 1-4 weeks post transplantation with at least two of the following conditions: jaundice, weight gain, right upper quadrant pain, hepatomegaly, ascites, and encephalopathy.

Chronic RILD The liver usually heals after the subacute RT injury, but chronic fibrosis may develop depending on the degree of RT and chemotherapy injury. When fully expressed, the damage resembles finely nodular cirrhosis both pathologically and clinically. Irradiation to parts of the liver can cause localized fibrosis with no clinical sequelae of hepatic insufficiency if the consequent hypertrophy/hyperplasia of the untreated organ provides sufficient functional compensation.

Management No established therapies exist for RILD, although the use of anticoagulants and steroids has been suggested. The majority of patients with this syndrome also respond to conservative diuresis. There are also no established therapies for CMILD.

ESOPHAGUS

Acute effects Symptoms of gastroesophageal reflux with dysphagia develop approximately 2 weeks following initiation of RT. Early RT esophagitis is generally the dose-limiting reaction in aggressive multimodality therapy, as is used for esophageal and lung cancers. Decreased mucosal thickness may progress to frank ulceration, which may heal with fibrosis and cause benign strictures. Amifostine significantly decreased severe esophagitis in lung cancer patients treated with chemoradiation therapy in phase III randomized trials from 26.0% to 6.5% ($P = .038$).

Analgesics, topical anesthetics (see previous section on "Oral mucosa"), sucralfate, H_2-receptor blockers (ranitidine, cimetidine, famotidine), omeprazole (Prilosec), antacids, or metoclopramide are used for symptomatic relief. Sucralfate slurry may also be used prophylactically, before and after RT daily to reduce the severity of esophagitis, and may promote healing (see also the pharynx and esophagus section under "Head and neck ").

Late effects Formation of benign strictures and changes in motility secondary to muscle and/or nerve damage cause chronic dysphagia. Strictures develop a median of 6 months after RT and generally are not seen before 3 months. Strictures are dilated with Maloney or Savory dilators. Prokinetic drugs, such as metoclopramide, can lessen gastroesophageal reflux by increasing lower

esophageal sphincter pressure and the rate of gastric emptying. Cisapride (Propulsid) also increases GI motility.

Effects of chemoradiation therapy Such drugs as cisplatin, 5-FU, dactinomycin (Cosmegen), doxorubicin, bleomycin, and methotrexate can augment the acute effects of RT on the esophagus, but the effect of these agents on late complications is not yet well established.

STOMACH

Acute effects Acute nausea and vomiting can occur shortly after the daily delivery of RT. Gastric secretions are suppressed acutely but recover later. Erosive and ulcerative gastritis can develop 2-3 weeks after RT begins but is generally transient and abates rapidly after the completion of RT.

Use of antiemetics (eg, ondansetron [Zofran], metoclopramide, prochlorperazine, granisetron [Kytril], dronabinol [Marinol], lorazepam, and chlorpromazine) and a decrease in the RT daily dose per fraction may ameliorate acute nausea and vomiting. Antiemetics begun within an hour before RT delivery may prevent the nausea and vomiting that may occur shortly after such therapy.

Late effects of irradiation on the stomach include the following conditions:

Dyspepsia arises at 6 months after RT (range, 2-20 months) as vague gastric symptoms.

Gastritis develops at 12 months after RT (range, 1-48 months) and is accompanied by radiologic evidence of spasm or stenosis of the antrum. The pathologic basis is fibrosis of the submucosal tissue, leading to mucosal fold smoothening and atrophy.

Ulceration typically arises at 5 months after RT (range, 1-72 months). Radiation-induced ulcers are indistinguishable from peptic ulcers. Spontaneous healing may occur but can be accompanied by submucosal fibrosis, which can produce antral fibrosis. Progressive stomach contracture results in early satiety, anorexia, and weight loss.

Ulcer with perforation may develop at 2 months after RT (range, 1-30 months).

Late RT toxicities have been treated with H_2-receptor antagonists and sucralfate. Surgery (eg, partial gastrectomy) is utilized for perforation, bleeding, or gastric outlet obstruction.

In a multicenter trial, patients with colorectal cancer treated by surgery followed by 5-FU chemotherapy (C) and radiation therapy (RT, 50-60 Gy) were randomized to receive above treatment ± amifostine. Blood counts and gastrointestinal acute toxicity were evaluated weekly during CRT. Patients treated with CRT plus amifostine had a significantly lower incidence of intestinal (grade ≥ 2) toxicity during treatment. Three months after therapy, patients treated with amifostine had a significantly lower incidence of intestinal toxicity (5.6% vs 22.2%, $P = .0112$; *Antonadou D, Athanassiou H, Sarris G: Proc Am Soc Clin Oncol [abstract] 22:293, 2003*).

SMALL AND LARGE INTESTINES

The tolerance of the small and large intestines is a major dose-limiting factor in the treatment of many cancers of the abdomen and pelvis.

Acute effects Nausea, vomiting, early satiety, anorexia, and fatigue are frequent acute effects. Nausea and vomiting may develop shortly after RT delivery, necessitating the use of prophylactic antiemetics. Acute proctocolitis in patients undergoing pelvic RT is extremely common, manifesting clinically as watery bowel movements with rectal urgency and tenesmus. Patients receiving RT following low anterior resection experience frequent small stools since the rectal vault capacity is markedly diminished. Hematochezia occurs infrequently and is often due to hemorrhoidal irritation.

Radiation enteritis develops if significant volumes of small bowel are irradiated. Symptoms appear 2-3 weeks after the initiation of RT, and the enteritis increases in severity until several days after treatment is discontinued. Loose to watery diarrhea with voluminous frequent stools and cramping abdominal pain are characteristic of fully developed enteritis.

Management Diarrhea is treated with a low-residue diet and loperamide or diphenoxylate, 1-2 tablets PO qid prn. Psyllium is sometimes helpful, as is cholestyramine (Questran, Prevalite). *Clostridium difficile* infection should be ruled out. Octreotide (Sandostatin; a long-acting analog of somatostatin) at 0.1 mg SC tid was compared with diphenoxylate in a randomized trial and was found to be more effective in controlling diarrhea induced by pelvic irradiation.

Similarly, proctitis may be treated according to the prevailing problem. Anusol-HC cream or Anusol suppositories are effective for alleviation of local symptoms of proctitis, such as tenesmus. Oral sucralfate may promote healing of proctitis. Mesalamine suppositories and glucocorticoid retention enemas may be used for unresponsive proctitis and sulfasalazine for associated bleeding. (For management of nausea and vomiting, see previous section on "Stomach.")

Late small bowel effects The median onset of late small bowel RT effects is 1-5 years following the completion of RT and may be hastened by concomitant chemotherapy. Obstruction, the most common late effect, is preceded by sporadic or gradually increasing episodes of acute colicky abdominal discomfort. Perforation presents with an acute abdomen. Occasionally, late bowel damage is manifested by massive bleeding. Radiographic findings include fibrosis and ischemia. Spasm is seen, with altered bowel transit times, ulceration, thickened folds, narrowed bowel segments, and marked mesenteric adhesions.

Malabsorption is a common sequela of the late changes of RT and can include bile salt wasting from extensive ileal involvement. Stasis predisposes to bacterial overgrowth. Enterocolonic fistulae can also cause massive intraluminal bacterial overgrowth with severe steatorrhea and vitamin B_{12} deficiency.

Late large bowel injury becomes manifest earlier than late injury to the small bowel (within 2 years of treatment; median, 6-18 months). Fistulae occur more often in the rectum than elsewhere in the gut and are confined almost exclusively to cases in which brachytherapy was used for gynecologic cancer. They usually occur along the anterior rectal wall posterior to the vaginal fornix.

Other chronic symptoms include strictures, tenesmus, bleeding, cramps, obstipation, diarrhea, and rectal urgency; surgical intervention is sometimes

necessary if these symptoms become severe enough. Radiographically, the most frequent appearance of large bowel injury is a smooth, elongated narrowing. Alternatively, submucosal changes can give the appearance of a nodular or thumbprinting effect on the large bowel wall. Mesenteric shortening can produce retraction of the transverse colon.

Ulceration is frequent and sometimes simulates diverticulitis. Bleeding can occur from sites of ulceration and telangiectasis.

Management Mild cases of chronic RT injury to the small and large intestines can be managed by a low-residue diet, stool softeners, psyllium, loperamide, or diphenoxylate. Fiber laxatives give a firmer consistency to the stool and soften it. Cholestyramine can improve diarrhea due to small bowel injury by binding bile salts that are irritative to irradiated bowel. Bleeding from sites of ulceration and telangiectasis can be treated by endoscopic laser therapy. Patients with malabsorption may benefit from pancreatic enzymes (eg, Pancrease) or lactase enzymes (eg, LactAid). Flatulence may be treated with simethicone. Pentoxifylline increases blood velocity and may promote healing. Again, mesalamine suppositories and glucocorticoid enemas may be helpful, as may sulfasalazine.

Surgical management for late bowel complications is controversial. Some investigators favor an aggressive approach, with lysis of all adhesions to free up the full length of the small bowel and resection of all severely involved segments. Others advocate a much more conservative approach of bypassing injured bowel by the simplest procedure possible.

Effects of chemoradiation therapy Dactinomycin or concurrent doxorubicin enhances the risk of late intestinal complications. Bolus infusion of 5-FU, which is included in most chemoradiation therapy regimens, has not been shown to increase the risk of late intestinal complications. High-dose infusional 5-FU, however, may enhance the risk of late intestinal complications.

Thyroid

HYPOTHYROIDISM

Primary hypothyroidism may be seen in patients who have received therapeutic RT doses to the cervical area. Subclinical hypothyroidism is the most common finding, with clinical hypothyroidism seen less frequently. The cumulative risk of developing overt or subclinical hypothyroidism is approximately 50%, and half of this risk manifests within 5 years of therapy. The use of iodinated radiographic contrast agents prior to RT, especially the ethiodized oil emulsion used in lymphangiography in Hodgkin's lymphoma and other lymphomas, has been proposed as a contributing factor.

Hypothyroidism has been documented after irradiation to the craniospinal axis for CNS tumors, after total-body RT for BMT, and after RT for Hodgkin's lymphoma or head and neck malignancies.

Hypothyroidism may develop as the result of thyrotropin (thyroid-stimulating hormone [TSH]) deficiency or hypothalamic injury following RT for pituitary

adenomas, brain tumors, or head and neck cancers. Thyrotropin deficiency may be the sole manifestation of pituitary injury or may be accompanied by loss of corticotropin, gonadotropins, and growth hormone.

HYPERTHYROIDISM

Thyrotoxicosis (Graves' disease) may also develop after external irradiation of the thyroid, as seen in patients with Hodgkin's lymphoma. These patients develop hypothyroidism after several months.

THYROID ENLARGEMENT, NODULARITY, AND DEVELOPMENT OF NEOPLASMS

Hashimoto's thyroiditis has been observed after RT of the thyroid in patients with Hodgkin's lymphoma. Persistently elevated TSH levels result in hyperstimulation of the thyroid gland with development of nodules (adenomas or carcinomas). The actuarial risk of developing thyroid cancer after RT has been reported to be 1.7, as compared with an expected risk of 0.07% in the normal population matched for age and sex. The relative risk of developing thyroid cancer after RT for Hodgkin's lymphoma is approximately 15.6 (95% confidence interval [CI], 6.3-32.5), and the absolute risk is 33.9 cases per 100,000 person-years.

Management Serum TSH levels and free thyroxine (FT_4) should be determined annually, and levothyroxine sodium should be prescribed for subclinical hypothyroidism. Cancer risk may also be reduced by limiting the effects of TSH on RT-damaged thyroid follicles. (For further discussion of thyroid nodules and thyroid carcinomas, see chapter 5.)

Hematopoietic stem-cell compartment

Acute effects Lymphopenia occurs almost immediately after RT because lymphocytes are exquisitely sensitive and die in interphase. Neutropenia occurs in the first week after irradiation of large volumes of bone marrow, followed by thrombocytopenia in 2-3 weeks and anemia in 2-3 months.

A rapid depletion of vital stem cells occurs within 1 week following appropriate total-body doses. The microvasculature usually survives the conventional doses used for total-body RT and allows the implantation and proliferation of transferred stem cells, resulting in recovery. Acute effects are not usually seen unless a substantial portion of bone marrow is treated. RT is usually not commenced if the absolute neutrophil count is $< 1.5 \times 10^3/\mu L$, with platelets $< 75 \times 10^3/\mu L$. A hemoglobin value of 10 g/dL is desirable during RT. Adequate oxygenation increases tumor radiosensitivity.

Permanent ablation or hypoplasia The capacity of the unexposed bone marrow to compensate by accelerating its rate of hematopoiesis is sufficient when the RT field involves < 10%-15% of the bone marrow. When 25%-50% of bone marrow is irradiated, permanent ablation or hypoplasia also occurs at similar dose levels as for small fields. The unirradiated marrow becomes hyperactive to meet the demands for hematopoiesis.

When 50%-75% of the bone marrow is irradiated, hematopoietic activity increases in the unexposed marrow segments, followed by extension of functioning marrow into previously quiescent areas. Although hematopoietic stem cells are exquisitely radiosensitive, it is damage to the bone marrow stroma that primarily accounts for chronic RT injury. Irreversible injury after RT is a consequence of irreparable damage to the microvasculature, manifested by irrevocable bone marrow fibrosis.

Management Treatments for bone marrow injury include transfusions of erythrocytes, platelets, and possibly granulocytes in patients who have severe neutropenia (< 200/μL) and documented infections that have not responded to appropriate antibiotics. Administration of growth factors is a common supportive measure in patients with RBC or WBC deficiencies. Epoetin alfa (Epogen, Procrit) has been used for anemia, granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) has been used for neutropenia, and oprelvekin (Neumega) has been given for thrombocytopenia. The American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) recommend epoetin alfa for anemia, with hemoglobin levels < 10 g/dL, related to cancer treatment. The use of epoetin alfa for anemia (10-12 g/dL) should be determined by clinical circumstances. Darbepoetin alfa (Aranesp) is longer acting, allowing less frequent dosing. Peripheral blood stem-cell transfusions are effectively used as an alternative to autologous BMT. Allogeneic BMT is an obvious approach to restoring marrow function in patients with chronic marrow failure.

Effects of chemoradiation therapy When RT and chemotherapy are administered concurrently and sufficient time is allowed for recovery of peripheral blood cell counts (1-2 months), the increased marrow toxicity of the second modality reflects the irreparable damage caused by the first modality. The potential effects of chemoradiation therapy are much more complicated when both modalities are used simultaneously.

Bone

Inhibition or impairment of skeletal growth is an important dose-limiting toxicity of ionizing radiation, especially in children. Few attempts have been made to quantify RT-related growth arrest or to develop consistent methods for assessing its impact on function and cosmesis. Consequently, the impact of various treatments and the influence of clinical interventions once complications have developed have been difficult to evaluate.

Axial skeletal growth arrest may be terminated by irradiation, resulting in disproportionate sitting and standing heights.

Scoliosis can be caused by partial RT of vertebral bodies, soft-tissue asymmetry caused by surgery, and RT-induced hypoplasia of the rib cage and pelvis. Failure to correct leg-length discrepancies can also cause back problems, including scoliosis.

Slipped capital femoral epiphysis has also been reported as a complication of hip RT in children.

Abnormalities of craniofacial growth can cause significant cosmetic and functional deformities.

Management Careful RT technique to exclude the epiphyseal growth plates can minimize the risk of serious late effects. Early intervention can prevent secondary progressive injury and improve the functional result of treatment in the fully grown individual.

Mild asymptomatic scoliosis may be treated conservatively. Physical therapy and exercise programs can be helpful. In cases of severe back pain and spinal curvatures – 20°, braces may improve support. Surgical intervention with placement of a Harrington rod is recommended only for severe cases.

Appropriate shoe lifts can correct leg-length discrepancies. Prompt recognition of capital femoral epiphysis slippage is extremely important. Surgical treatment typically consists of pinning, but severe cases may require osteotomy and osteoplasty.

Nerves and muscles

PERIPHERAL NERVES

Peripheral nerve damage from RT is rare, but latency is important in its evaluation. Peripheral nerve damage has been seen following intraoperative RT and appears to be the dose-limiting toxicity in many cases. Cranial nerve injury is not usually seen.

Brachial plexopathy increases in incidence when large daily RT doses are used and is sometimes reported after axillary RT (eg, for breast cancer). Breast cancer patients who have received chemotherapy have a higher incidence of brachial plexopathy than those receiving RT only.

Sacral plexus injuries after RT for carcinoma of the cervix have also been reported occasionally.

MUSCLES

Late complications include limb contracture, edema, decreased range of motion, pain, and decreased muscle strength. They may be of minor or severe functional importance. Latency is important in the evaluation of muscle injury since progression may continue for as long as 10 years after RT. Chemotherapy does not seem to have a major impact on the incidence of late soft-tissue injury but does increase the rate of acute reactions.

Management is aimed at decreasing the size of the RT field, thereby sparing more functional healthy tissue, as long as cure is not compromised. Vigorous physical therapy and rehabilitation during and especially after RT are important. Muscle relaxants, eg, cyclobenzaprine (Flexeril), and anxiolytics, such as lorazepam, are useful for muscle spasms. Pentoxifylline may be tried to improve blood flow velocity and promote healing.

Neuroendocrinologic system

Growth hormone deficiency, the most common RT-induced endocrine disturbance, is most evident in the growing child as a reduction in growth velocity. In the postpubertal individual, growth hormone deficiency is associated with a relative decrease in muscle mass and an increase in adipose tissue.

Gonadotropin deficiency Young children may fail to enter puberty, and females may experience primary amenorrhea. Adult deficiency may be associated with infertility, sexual dysfunction, and decreased libido.

Early sexual maturation Precocious puberty may be seen in patients who have received cranial RT.

TSH deficiency Excessive weight gain and lethargy can be seen with complete TSH deficiency of long duration. Children may have poor linear growth and delayed puberty.

Adrenocorticotropic deficiency and hyperprolactinemia may also be seen.

Kidneys

A number of overlapping clinical syndromes are recognized, depending on the renal volume irradiated and the RT dose delivered.

Radiation nephropathy Acute radiation nephropathy (up to 6 months) following RT is rarely symptomatic; the glomerular filtration rate may be decreased. Signs and symptoms in the subacute period (6-12 months) include dyspnea on exertion, headaches, ankle edema, lassitude, anemia, hypertension, elevated blood urea levels, and urinary abnormalities. Benign or malignant hypertension is seen in the chronic period (generally after 18 months), depending on the severity of renal damage.

Chronic radiation nephropathy, in its mildest forms, may not be diagnosed for many years after RT. The only abnormalities may be proteinuria and azotemia with urinary casts or mild hypertension. A contracted kidney is seen on IV pyelography. Death may occur from chronic uremia or left ventricular failure, pulmonary edema, pleural effusion, and hepatic congestion.

Other syndromes More recently, hyper-reninemic hypertension has been described following unilateral renal RT, as has the nephrotic syndrome.

Management Hypertension and peripheral and pulmonary edema should be treated actively with appropriate medications, and anemia should be corrected. Renal tubular function may show some recovery. Dialysis and transplantation are sometimes necessary.

Effects of chemoradiation therapy Combined-modality treatment appears to intensify RT-induced renal changes.

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